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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/692,382	10/22/2003	David W. Morris	529452002420	1189

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EXAMINER	
KIM, YOUNG J	

ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/692,382	MORRIS ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49 and 55-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49 and 55-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicants' election of invention for prosecution is in two parts as follows:

In response to the restriction requirement mailed on March 21, 2008, Applicants have elected for prosecution, the invention defined by Group XIV, drawn to methods for diagnosing cancer by polynucleotide level detection, in the Election received on September 22, 2008.

This election has been treated as an election without traverse because Applicants did not distinctly and specifically point out the supposed errors in the restriction requirement (MPEP § 818.03(a)).

In response to the species requirement mailed on October 17, 2008, Applicant's election with traverse of Species i, drawn to a method of diagnosis drawn to colon cancer is acknowledged. The traversal is on the ground(s) that a thorough search of the elected species will include art relevant to the non-elected species. Applicants' rationale is that a search of determining the expression of B5 gene would reveal art relevant to those which are correlated with all types of cancer (page 2, 2nd paragraph, Response). This is not found persuasive because as it was specifically pointed out, the species are clearly patentably distinct and independent. A correlation of differential expression in a particular gene to a particular cancer does not render obvious a differential expression of the same particular gene to another cancer. A search for all types of cancers for correlation will result in a clear search burden as search and examination requires not only for prior art, but also for the state of the art (for enabling disclosures).

The requirement is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

No IDS has been filed to date of the instant Office communication.

Specification

Applicants are advised that the Abstract should reflect the elected invention. The elected invention is drawn to a method of diagnosis via polynucleotide detection.

The specification is objected to for not identifying the U.S. Application Serial Number from which the present application claims priority. Applicants are invited to amend the specification to correct the deficiency. As neither ADS nor the specification discloses the actual U.S. Application serial number of the parent application, Applicants are invited to supply evidence that the U.S. Application serial number is assigned the attorney docket no. identified on section [0001] of the instant application (Attorney docket no. 52945-20024.33).

The specification is objected to for failing to comply with the Sequence Rules as set forth in the 37 CFR 1.821-1.825 which requires that any amino acid sequence disclosure which are more than 4 contiguous amino acids in length (1.821(a)) must be accompanied by a SEQ ID Number.

Section [0072] of the instant application contains the sequence, "WSXWS."

Applicants are invited to comply with the sequence rules for the disclosure therefore.

Drawings

The drawings received on October 22, 2003 are acceptable.

Claim Interpretation

Applicants' election is drawn to a particular type of cancer, the cancer being colon cancer. The claims have been examined to the extent of their elected subject matter therefore.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 49 and 55-73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 49 is indefinite as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01.

Claim 49 simply recites that the expression level of cytochrome B5 gene is determined from a first tissue type of a first individual and compared against that of a second normal tissue type of the same individual or a second unaffected individual. Claim 49 omits what the first tissue type is or whether or not the first individual is suffering or suspected of having cancer.

In addition, claim 49 recites, "unaffected" individual, but fails to clearly limit what the first individual is affected with. While the claim preamble recites that the method is drawn to diagnosis of cancer, the actual steps do not recite any real limitation drawn to cancer diagnosis, but a simple comparison of cytochrome B5 gene level between two samples.

Claim 55 recites the term, "normal control." It is unclear what is meant by this limitation. For the purpose of prosecution, the term is assumed to mean that which is not cancerous.

Claims 56-59 are indefinite by way of their dependency on claim 55.

Claim 60 is indefinite for failing to recite a final process step which agrees back with the preamble. While minor details are not required in method/process claims, at least the basic steps must be recited in a positive, active fashion. See *Ex parte Elrich*, 3 USPQ2d, p. 1011 (Bd. Pat App. Int. 1986). For example, claim 60 is drawn to a method of diagnosing cancer, yet the claim recites only an active step of comparing the expression level of cytochrome B5 gene between two samples.

While the claim does have a limitation followed by the term, "wherein," the limitation is not deemed an active correlation step and thus provides no patentable weight thereto.

Claims 60-67 are indefinite by way of their dependency on claim 60.

Claims **49 and 55-73** are indefinite analogously. Amending the claims to require an active correlation step would overcome this rejection.

Claim 60 is indefinite because the claim recites that a differential expression of cytochrome B5 is detected, but fails to recite to what the cytochrome B5 of level from a patient sample is being compared against. For the purpose of prosecution, it is assumed that the differential expression is derived by comparing against a non-cancerous cancer sample.

Claims 61 and 65-67 are indefinite by way of their dependency on claim 60.

Claim 68 is indefinite for reciting the phrase, "highly stringent conditions."

While the term, "stringent condition" may be broad encompassing all possible hybridization conditions (e.g., low, moderate, and high and any intervals therebetween), when the limitation calls for, "highly stringent" conditions, it connotes that one of skill in the art would know what conditions are deemed low, moderate, high, and any intervals therebetween. However, without a specific definition in the specification which limits the term, "highly stringent condition" to a particular set of conditions, one of skill in the art would not know when the conditions will stop being low, moderate, or high. Therefore, the usage of the present limitation is deemed indefinite.

Claim 68 is indefinite because the limitation defining the hybridization found on the last line of the claim is ambiguous as to which hybridization it is referencing. Claim 68, step (a) employs a polynucleotide that "hybridizes" to SEQ ID Number 869 as well as hybridization step which implicitly occurs in step (b) in the phrase, "duplex formed."

Claim 69 recites the phrase, "control." It is unclear what is deemed a "control."

For the purpose of prosecution, the control is assumed to mean non-cancerous sample. Claims 70 and 71 are indefinite by way of their dependency on claim 69.

Claim 72 recites the phrase, "control colon sample." It is unclear what is deemed to mean "control colon sample." For the purpose of prosecution, the phrase has been assumed to mean non-cancerous sample.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 49 and 55-67 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a **New Matter** Rejection.

Claim as originally filed on October 22, 2003 does not disclose that SEQ ID NO: 869 as being cytochrome B5 gene and the specification as originally filed does not contain this characterization.

The first characterization of the nucleic acid of SEQ ID NO: 869 as being cytochrome B5 gene occurs in the Amendment received on September 22, 2008, in response to the restriction requirement mailed on March 21, 2008.

Applicants point to sections [0084] and [0085] as well as Table 93 for support of the claim language found on claim 49 (the sole pending independent claim). Sections [0084] and [0085] contain descriptions for generalized teachings regarding nucleic acid hybridizations and their

conditions, but none in regards to SEQ ID NO: 869. The Table 93, to which Applicants reference to cannot be found. The only Table which contains some description regarding the SEQ ID Numbers is Table 50 and none of the genes characterized on this table contains SEQ ID NO: 869 nor characterization of any nucleic acids being cytochrome B5.

Lastly, the sequence listing only identifies SEQ ID NO: 869 as that which is isolated from "homo sapiens."

Therefore, claims which are drawn to the method of detection wherein the nucleic acid is cytochrome B5 contain new matter, and thus, should be removed.

Claims 49, 55-70, and 73 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The following is a **Written Description** Rejection.

The written description requirement ensures that, "an applicant invented the subject matter which is claimed. Further, the written description requirement for a claimed genus may be satisfied *through a* sufficient description of *a representative number of species* by 1) reduction to practice; 2) reduction to drawing; or 3) disclosure of relevant identifying characteristics (*i.e.,* structure of other physical and/or chemical properties, functional characteristics *coupled* with a known or disclosed correlation between function and structure) (MPEP 2163 at II(A)(3)(a)(ii)).

Reduction to Practice

Claims are drawn to a method of diagnosing a colon cancer via determining the expression of a cytochrome B5 gene in a first tissue type of a first individual and comparing said expression from a second normal tissue type from said first individual or a second unaffected individual. It is known in the art that cytochrome B5 exists in different types, such as type A, B, etc. (see publication from Santa Cruz Biotechnology, available on the web: http://www.scbt.com/datasheet-105265-cytochrome-b5-type-b-sirna-h.html, retrieved on January 2, 2009, provided herein), as well as different types of cytochrome B5, such as type 2 cytochrome B5 (Soucy et al., The Journal of Steroid Biochemistry and Molecular Biology, January 2002, vol. 80, no. 1, Abstract, provided herein).

The instant application contains description for a method of determining a colon cancer which involves the determination of expression level of a polynucleotide comprising SEQ ID NO: 869.

The instant application does not contain any description for the same method employing any of its homologs, nor does the specification even contain any description pertaining to any cancer diagnosis by looking at expression level of different types of cytochrome B5, or any cytochrome B5 gene for that matter.

Reduction to Drawing

The instant application contains no drawings pertaining to a method of diagnosing a colon cancer by determining the expression levels of cytochrome B5 gene or any types of cytochrome B5 genes, or any homologous sequences of SEQ ID Numbe 869.

Disclosure of Relevant Identifying Characteristics

With regard to the homologous nucleic acid sequences of SEQ ID NO: 869, while one could argue that a skilled artisan would be able to identify the "representative number of species" by

employing nucleic acid of SEQ ID NO: 869 to identify its homologous sequences, mere wish to isolate the homologous sequences are not a proper demonstration of possession.

As stated in *University of California v. Eli Lilly and Co.* at page 1404:

> An adequate written description of a DNA ... "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. *Fiers v. Revel*, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, ***"an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it***, what is required is a description of the DNA itself." *Id.* at 1170, 25 USPQ2d at 1606.

Therefore, for the foregoing reasons, the claims are not properly described for a method of diagnosing cancer by determining the expression level of cytochrome B5, or any homologous sequences of SEQ ID NO: 869.

Claims 49 and 55-73 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure would require undue experimentation are summarized in In Re Wands (858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)). They include (A) the quantity of experimentation necessary, (B) the amount of direction or guidance presented, (C) the presence or absence of working examples, (D) the nature of the invention, (E) the state of the prior art, (F) the relative skill of those in the art, (G) the predictability or unpredictability of the art, and (H) the breadth of the claims.

The Breadth of the Claims and & Enablement Issues:

The claims are broadly drawn to a method of diagnosing carcinoma or a propensity for carcinoma by comparing the expression of a nucleotide having 95%-99% sequence identity to SEQ ID NO: 869 in one sample with another sample from a normal tissue type.

The instant specification disclose that there are a number of viruses known to be involved in human cancer as well as in animal cancer and the ones of particular interest are viruses that do not contain oncogenes themselves, which induce tumors by integrating into the host genome and affecting neiboring protooncogenes in a variety of ways (section [0006]).

The instant specification discloses that with respect to lymphoma and leukemia, retroviruses such as AKV murine leukemia virus (MLV) or SL3-3 MLV, are potent inducers of tumors when inoculated into susceptible newborn mice, or when carried in the germ line and with respect to cancers, especially breast cancer, prost cancer and cancers with epithelial origin, the mammalian retrovirus, mouse mammary tumor virus (MMTV) is a potent inducer of tumors when inoculated into susceptible newborn mice, or when carried in the germ line.

The instant specification states that the instant invention is directed to a number of sequences associated with cancers, especially lymphoma, breast cancer or prostate cancer based on the "relatively tight linkage between clonally-integrated proviruses and protooncogenes" in that uninfected animals have low cancer rates, and infect animals have high cancer rates (section [0040]).

The specification states that the use of oncogenic retroviruses, whose sequences insert into the genome of a host organism resulting in cancer, allows the identification of host sequences involved in cancer. (section [0041]).

Based on this finding, the specification concludes:

"However, as it will be appreciated by those in the art, oncogenes that are identified in one type of cancer such as lymphoma or leukemia having a **strong likelihood of being involved in other types of cancers as well**." (section [0041])

The question of enablement is risen because the application has no data to support this general hypothesis that simply because there is a "strong likelihood" of an oncogene, which is involved in leukemia, being involved in other types of cancers, one of skill in the art would accept without question that any nucleic acid sequence involved in leukemia can be employed for diagnosis of other types of cancers, for the purpose of examination herein, colon cancer (the elected subject matter) and thus make and use the invention as claimed without undue experimenation.

Amount of Guidance:

The specification contains generalized description pertaining to detection of cancer, such as those employing hybridization detection (pages 46 and 56-64), immunoassays (pages 78-81).

The specification while disclosing that CA nucleic acids (whose list contains hundreds of SEQ ID Numbers, see Table 1 for example) can be downregulated or upregulated (in general), simply fails to disclose which of the nucleic acids are upregulated or downregulated for a particular cancer (for the present application, colon cancer).

In addition, the specification, simply has no data which would convey to one of skill in the art that the expression level of polynucleotide of SEQ ID NO: 869 or any of its homologs are implicated with colon cancer. There is simply guidance for the claimed invention other than general teachings of cancer diagnosis by nucleic acid hybridization which can be applied for any nucleic acids in general.

Working Examples:

There are no working examples for the method of diagnosing colon cancer by differential expression detection of cytochrome B5 or the polynucleotide of SEQ ID NO: 869 or its homologous sequences.

The state of prior art:

Those of skill in the art would also recognize that the diagnosis of cancer using specific biomarkers has many variables prior to any type of predictive success. Tockman et al. (Cancer Research, 1992, vol. 52, pages 2711-2718) teaches considerations necessary to bring a cancer biomarker to successful clinical applications. Prior to the successful application of newly described markers, research must validate the markers against acknowledged disease and end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective populations trials (Abstract). Early stage markers of cacinogenesis have clear biological plausibility as markers of preclinical cancer and if validated can be used for population screening (page 2713, 1st column). The artisans further express that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed) cancer outcome.

Clearly, prior to successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials (page 2716, 2nd column).

Lucentini et al. (The Scientist, 2004, vol. 18), share the importance of exercising cautions when implicating a biomarker with a particular disease, who titled his article, "Gene Association Studies Typically Wrong," and stating, "[t]wo recent studies found that typically, when finding is first published linking a given gene with a complex disease, there is only roughly a one-third chance that studies will reliably confirm the finding (page 2 of the print out).

This is consistent with the teachings of Wacholder et al. (Journal of National Cancer Institute, 2004, vol. 96, no. 6, pages 434-442) who notes that, "[t]oo many reports of association between genetic variants and common cancer sites and other ***complex diseases*** are false positives (see Abstract).

Skill Level & Unpredictability:

The instant invention, as claimed, falls under the "germ of an idea" concept defined by the CAFC. The court has stated that "patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may be workable". The court continues to say that "tossing out the mere germ of an idea does not constitute an enabling disclosure" and that "the specification, not knowledge in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement". (See *Genentech inc v. Novo Nordisk A/S* 42 USPQ2d 1001, at 1005). As Applicants' invention is derived from the hypothesis that cancers which are involved in leukemia have a strong likelihood of being involved in other cancers, such "germ of an idea," as the court expressed, is only a vague intimation that may or may not workable. Such "tossing out of" hypothesis would not constitute an enabling disclosure.

And as also set forth in *Rasmusson v. SmithKline Beecham Corp.*, 75 USPQ2d 1297, 1302 (CAFC 2005), enablement cannot be established unless one skilled in the art "would accept without question" an Applicant's statements regarding an invention, particularly in the absence of evidence regarding the effect of a claimed invention. Specifically:

> "As we have explained, we have required a greater measure of proof, and for good reason. If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."

Therefore, while the skill level of a skilled artisan is deemed high, as already discussed above, cancer is a highly complex disease involving a plurality of factors which are highly variable. Thus, based on the foregoing reasons, it is determined that one of skill in the art would not be able to practice the invention as claimed without undue experimentation.

Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 9:00 a.m. to 5:30 p.m (M-F). The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Young J. Kim/
Primary Examiner
Art Unit 1637
1/9/2009

/YJK/